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Chemotherapy for Acute Lymphoblastic Leukemia May Cause Subtle Changes of the Spinal Cord Detectable by Somatosensory Evoked Potentials

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Intrathecal chemotherapy has been determined to cause transient or permanent paraparesis due to myelopathy in patients with leukemia or other malignancies. To systematically evaluate the effect of methotrexate on spinal cord function, somatosensory evoked potentials (SEP) were measured in children with acute lymphoblastic leukemia (ALL). A prospective evaluation was performed in 38 consecutive children aged 1.4–15.3 years with newly diagnosed ALL during treatment. Intrathecal methotrexate therapy was included in the therapy schedule of all patients as central nervous system (CNS) therapy in addition to intravenous chemotherapy in 19 standard risk patients and intravenous chemotherapy with cranial irradiation in 19 intermediate or high-risk patients. The measured conduction times were compared with those of 38 control children matched for age, height, and sex. A significant increase in the conduction time of the tibial nerve SEP was found between the Th12 level and the cortex in children with ALL after receiving intrathecal methotrexate therapy during the induction and CNS therapy phases when compared with their controls. The difference of the mean latencies was 1.45 ms (95% CI 0.39–2.51; $P < 0.01$). There was no significant delay in the median nerve SEP from the brain stem to the cortex, indicating that the conduction delay was in the area of the spinal cord exposed to intrathecal methotrexate. Moreover, the cortical amplitudes of the median nerve SEPs were significantly reduced when measured immediately after intravenous and intrathecal methotrexate and compared to the amplitudes measured after induction therapy in standard risk patients ($P = 0.001$). Intrathecal methotrexate with systemic chemotherapy causes a deterioration in the somatosensory pathways within the CNS, suggesting also spinal cord dysfunction in children with ALL in addition to the cerebral dysfunction described earlier.

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Key words: acute lymphoblastic leukemia, children, intrathecal methotrexate therapy, spinal conduction delay

INTRODUCTION

Intrathecal methotrexate is commonly used in the treatment of leukemia and other neoplasms infiltrating the central nervous system (CNS). This form of therapy has been performed in the treatment of childhood acute lymphoblastic leukemia (ALL) as a form of CNS therapy in addition to intravenous chemotherapy and cranial irradiation since the late 1960s [1]. It is, however, associated with neurologic complications and transient or permanent neurologic sequelae have been reported in a number of patients with or without CNS leukemia [2–11]. Pathological-anatomical lesions in the spinal cord or brain tissue caused by intrathecal methotrexate and structural changes in magnetic resonance images in transient or permanent paraplegia caused by intrathecal chemotherapy have been described in patients with leukemia or other neoplasms [6–12]. In spite of this, systematic evaluations of possible functional adverse effects of intrathecal chemotherapy on the spinal cord have not been performed by neurophysiological methods to our knowledge.

Children with ALL have symptoms of gross and fine motor clumsiness usually related to vincristine neuropathy affecting peripheral nerves [13–15]. These difficulties may, however, be partly of spinal or brain tissue origin due to CNS therapy, including intrathecal and intravenous methotrexate therapy with or without cranial irradiation. Neurophysiological methods may be more sensitive in the detection of subtle myelin disruptions than are structural imaging techniques. Evoked potential methods have been utilized successfully in the detection of even subclinical demyelinating processes, e.g., multiple sclerosis [16]. The utility of sensory evoked potentials (SEPs) for the evaluation of localized spinal lesions, e.g., syringomyelia or spinal cord tumors, and functional disturbances of the sensory pathways in vitamin B12 deficiencies or in

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Friedreich ataxia has been verified [16]. To evaluate these side effects, we have measured the spinal and cortical evoked potentials to detect disturbances within the spinal cord and brain in children undergoing therapy for ALL.

SUBJECTS

The patient series included 38 consecutive children, 14 boys and 24 girls, admitted to the Department of Pediatrics, University of Oulu, from February 1986 to August 1989 for initial treatment of ALL and who achieved remission during the induction therapy. Their median age was 5.3 years (range 1.4–15.3) and all of them had normal developmental data, except that two had been born at 31 and 32 gestational weeks and had had birthweights of 2,090 g and 2,100 g, respectively. All the patients underwent follow-up clinical neurological examinations. The immunological cell types of leukemia were 36 non-T, non-B, 1 T-cell, and 1 unknown type. One patient had CNS leukemia at the time of diagnosis, with 10 blasts in her cerebrospinal fluid (CSF), but she also achieved remission and had no CNS or bone marrow relapses during treatment. None of the other patients had CNS leukemia during these measurements.

The patients were divided into three risk groups—standard risk (SR), intermediate risk (IR), and high risk (HR)—based on criteria used in all the Nordic countries [17]. The 19 patients with SR ALL were treated according to the Nordic regimen, in which remission was induced with prednisolone for 5 weeks, six weekly injections of vincristine (2 mg/m^2), three doses of doxorubicin (40 mg/m^2), and four intrathecal injections of methotrexate (12 mg/m^2) [17,18]. Consolidation and CNS therapies were performed with L-asparaginase and three pulses of intravenous methotrexate infusions (1,000 mg/m^2/24 hours) and three intrathecal doses, both at 3-week intervals. Subsequent therapy included 6-mercaptopurine daily and methotrexate weekly up to 36 months. The consolidation and CNS therapies were intensified after July 1986 by increasing the dose of L-asparaginase from 600 to 1,000 U/kg daily for 10 days, and by means of a reinduction therapy consisting of vincristine and prednisolone or intrathecal and intravenous methotrexate alternately every 4 weeks during the first year.

The 8 IR patients and 11 HR patients were treated according to the ALL-BFM 83 protocol [19], in which the induction therapy consisted of prednisolone, L-asparaginase, cyclophosphamide, cytosine arabinoside, and oral 6-mercaptopurine, as well as teniposide for the HR patients, in addition to four weekly injections of vincristine 1.5 mg/m^2 and four doses of daunorubicin (30 mg/m^2) and three doses of intrathecal methotrexate (8–12 mg). The delayed intensification and CNS therapies were performed with four pulses of intravenous methotrexate (500 mg/m^2) and intrathecal methotrexate, at doses of 8, 10, and 12 mg between the ages of 1 and 2, 2 and 3, and over 3 years, respectively, both at 2-week intervals. The CNS was also treated with radiation at doses of 18-24 Gy for 18 patients and 30 Gy for 1 patient, depending on the age and risk group. The delayed intensification therapy consisted of the same drugs as in the induction therapy, except that dexamethasone was administered in place of prednisolone. This therapy phase included two doses of intrathecal methotrexate. Subsequent therapy included oral methotrexate and 6-mercaptopurine.

The recordings of SEPs were performed on the 38 patients immediately after the induction therapy and after the delayed intensified and CNS therapies. At diagnosis, it was not possible to perform recordings before treatment, which was begun immediately. Neurological examinations according to Touwen were performed on all the patients at diagnosis and at the time of the recordings and form a separate report [15]. Three patients had slight neurological findings, one had speech disorders, one impaired hearing, and one impaired function of a facial nerve, which persisted during therapy. In addition to the clinical examinations, cranial computed tomography scans were performed on admission and 5 months after CNS therapy and the results have been reported earlier [20].

The SEP recordings were compared with those obtained for control children, and were individually matched for age, sex, and height. The mean heights of the SR patients and their controls were 110.5 and 110.2 cm, respectively, and those of the IR and HR patients and their controls were 119.6 cm and 119.3 cm, respectively. The controls were healthy children of the personnel of the University Central Hospital and they had normal developmental and neurological findings.

The investigation was carried out according to the provisions of the Declaration of Helsinki and approved by the ethical committee of the Faculty of Medicine, University of Oulu. Informed consent was obtained from the parents of both the patients and the control children.

METHODS

Equipment

The SEPs were recorded using a four-channel Disa 1500 D electromyograph which included a Disa 15 G 21 averager. The amplification of the electromyograph was set to 10 μV/div. The sampling frequency was 20 kHz for the median nerve SEP and 10 kHz for the tibial nerve SEP. Trials with excessive artifacts were automatically rejected. Latencies were measured on the oscilloscope screen with a cursor, and the pictures were then produced with an analogue x-y plotter. Amplitudes were measured subsequently on the printout.

Stimulation, Recording, Recording Techniques

The right median nerve was stimulated at the wrist with surface electrodes (Dantec^R 13L22 surface stimulation electrode) and the right posterior tibial nerve at the ankle. The stimulus intensity was adjusted to just over the motor threshold, so that it did not produce pain. The duration of the stimuli was 200 μs. The stimulation frequency was 1–4 Hz for the median nerve and 1–3 Hz for the tibial nerve. Disposable Ag/AgCl surface electrodes were used to record the responses (Dantec^R 13L20 surface electrodes). The analysis time was 50 ms for the median nerve SEPs and 100 ms for those of the tibial nerve. Two thousand readings were averaged in each case, and the procedure was performed twice.

For the median nerve SEPs, the active electrode in the first channel was placed on the left central (C_3) area, and linked ear electrodes (A_1A_2) were used as a reference (Ag/AgCl surface electrodes being placed on both earlobes and connected to the grid 2 in the amplifier). In the second channel, the active electrode was placed on the neck over the 7th cervical spinous process, and the reference electrode was placed on the midline of the forehead. In the third channel, the active electrode was placed on the neck as in the second channel, and the reference electrode on the anterior part of the neck. In the fourth channel, the active electrode was at the right Erb's point, and the reference electrode in the midline of the forehead. The bandpass was 2 Hz–1 kHz in the first channel, and 20 Hz–1 kHz in the other channels.

For the tibial nerve SEPs, the active electrode was placed 2 cm behind the C_4 location (C_4) in the first channel and 2 cm behind the Cz location (Cz′) in the second channel. Linked ear reference electrodes (A1A2) were used in the first and second channels. In the third channel, the active electrode was placed over the 12th thoracic spinous process, and the reference electrode over the christa. In the fourth channel, the active electrode was in the popliteal fossa, and the reference electrode was placed 4 cm above it. The bandpass was 2 Hz–1 kHz in the first and second channels, and 100 Hz–1 kHz in the third and fourth channels.

Measurements

The peak latencies of the P15 (brain stem), N20 (sensory cortex), and P25 (sensory cortex) components of the median nerve SEPs were measured from the first channel, the latency of the N13 peak (spinal potential from the C7 level) was measured from the third channel, and the latency of the EP peak (the compound action potential at Erb's point) from the fourth channel. If the P25 peak was two peaked, the latency was evaluated from the middle of the complex. The peak-to-peak N20-P25 amplitude was measured from the first channel.

The peak latencies of the P40 (sensory cortex) and N48 (sensory cortex) components of the tibial nerve SEPs were measured from the first or second channels and the latency of the SP peak (the spinal potential from the Th12 level) from the third channel. The peak-to-peak amplitude of P40-N48 was measured from the first or second channels.

The means of the latencies and amplitudes from both averages (averaging was performed twice on both sides) were calculated. The interpeak latencies (IPLs) EP-N13, N13-N20, and P15-N20 in the median nerve SEPs and SP-P40 in the tibial nerve SEPs were calculated from those means. Amplitudes were transformed to logarithms.

The measurements and calculations of the latencies in the children with ALL and their controls were studies by one of the authors, T. Kovala, a clinical neurophysiologist, who was unaware of which measurements represented patients and which controls.

The conduction times for the peripheral parts of the median and tibial nerve SEPs in these patients were delayed, indicating vincristine neuropathy, and have been discussed in another report [21].

Statistical Analysis

The data were organized and analyzed using the SAS computer program package (Statistical Analyses System Inc., Cary, NC). According to earlier experience, the SEP latency variables are fairly close to be normally distributed. Based on this assumption, the differences in mean latency within patients between the two measurements as well as between the patients and their controls were assessed with the paired *t* test and confidence intervals.

The measurements of SEP latencies of four SR patients could not be performed after the induction therapy for clinical reasons, so in within-patient comparisons these subjects were omitted, but they are included in the descriptive analysis of the patient group at the second measurement.

RESULTS

A delay was observed in the conduction time of the tibial nerve SEP between the Th12 level and the cortex ($P < 0.01$) in the children with ALL after receiving intrathecal and intravenous methotrexate therapy after two therapy phases (the induction therapy and CNS therapy). The delay was significant when compared with the conduction times of the age, height, and sex-matched control children (the data of these latencies are demonstrated in Fig. 1). A conduction delay was also observed by comparing the latencies after CNS therapy with those measured after induction therapy ($P = 0.01$; Table 1). There was no delay in the median nerve SEP from the brain stem to the cortex, indicating that the delay in conduction occurred within the spinal cord. There was no significant delay in the spinal conduction after the induction therapy

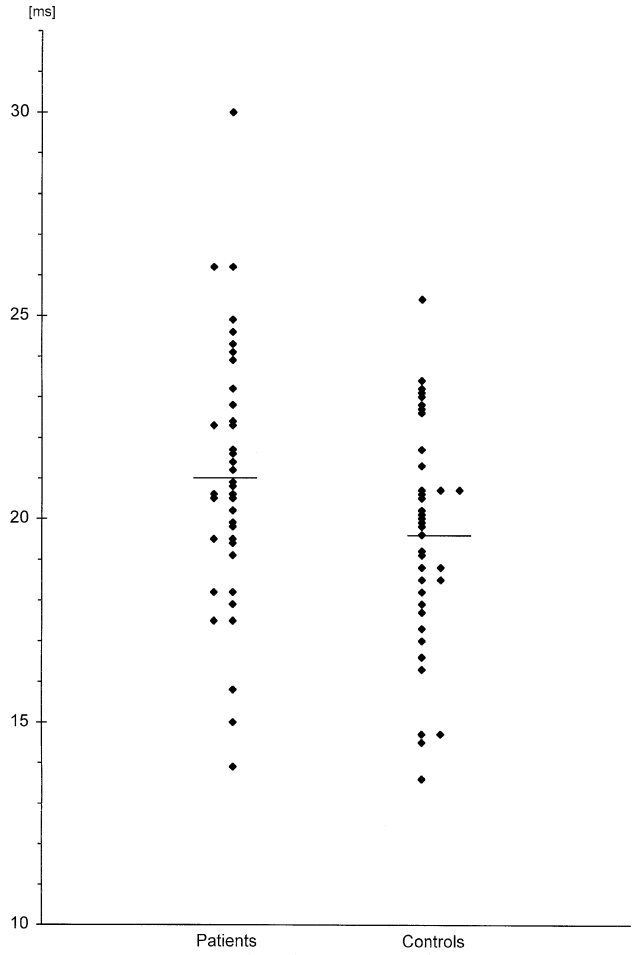

Fig. 1. The data of the latencies from the spinal Th12 to cortex (SP-P40) obtained from the patients after the two therapy phases (induction therapy and CNS therapy) and their controls. Lines show the means of the latencies.

in the entire patient group compared with the control children.

There was a conduction delay in the IR and HR patients in the spinal cord from the Th12 level to the cortex in the tibial nerve SEP, even after the induction therapy ($P < 0.02$) and the CNS therapy ($P < 0.02$), when compared with their control children. The differences in the mean latencies were 1.31 ms with a 95% CI of 0.29–2.32 and 1.80 ms with a 95% CI 0.33–3.27 ms, respectively. There were no significant delays in the peripheral or central conduction of the median nerve SEPs in these patients when compared with their control children, indicating a spinal conduction delay between the Th12 level and the brain stem. However, in this subset analysis there was a limited number of patients. The IR patients received three doses and the HR patients five doses of methotrexate intrathecally during the induction therapy and six additional doses during the CNS therapy. The IR patients received four and HR patients six intravenous methotrexate infusions of 500 mg/m^2, the total dose thus being 2 and 3 g/m^2, respectively.

There were no significant differences between the mean latencies and the IPLs of the SR patients and their control children after two therapy phases including seven doses of intrathecal methotrexate at 12 mg/m^2 and three intravenous methotrexate doses of 1,000 mg/m^2. A deterioration over the entire length of the measured CNS pathway from the Th12 spinal cord to the cortex ($P < 0.01$) was found in the tibial nerve SEP after CNS therapy when compared to the measurements after the induction therapy of the SR patients. The difference in the mean latencies was 2.63 ms with a 95% CI of 0.91–4.34 ms. In addition, the cortical amplitudes of the median nerve SEP were significantly decreased after CNS therapy (the mean N20/P25 amplitude decreasing from 5.65 to 3.23 μv; $P = 0.001$), and the cortical amplitudes of the tibial nerve SEP were not decreased during therapy.

Clinical Neurological Findings

Neurological examinations were also performed in all patients. Half of these patients were under the age of 5 years and exact sensory examinations were difficult to perform. Gross motor disturbances were observed in 9 patients after the induction therapy and in 13 patients after CNS therapy. Peripheral reflexes of the extremities were shown to be depressed after these therapy phases in almost all patients (35 of 38). This finding is suggestive of vincristine neuropathy [15]. The peripheral nerve latencies in both the median nerve SEP from the wrist to the brain stem ($P = 0.03$) and the tibial nerve SEP from the ankle to the cortex ($P < 0.001$) were delayed, which suggested the neurotoxic effect of vincristine. This effect was also observed in the patients between these two therapy phases, which both included vincristine, in the median nerve SEP from the wrist to cortex ($P < 0.01$). Somnolence syndrome was observed 5–8 weeks after irradiation in 11 of 19 patients, 8 of whom had impaired neurological findings [15].

DISCUSSION

Intrathecal therapy has been used for over 30 years and the adverse effects of this therapy on the spinal cord has not been properly evaluated. This is mainly due to the absence of methods suitable for this area. A variety of neurotoxic effects has been described. Chemical arachnoiditis shown in CSF changes is a well-known side effect of intrathecal therapy and the clinical symptoms of arachnoiditis (headache, meningismus and fever) are seen in 5–40% of the patients shortly after treatment [22,23]. Transient or permanent paraplegia after intrathecal therapy has been reported in individual patients with leukemia, and myelopathia has been demonstrated by magnetic resonance imaging [2–11]. Leukoencephalopa-

TABLE I. Mean (SD) Latencies (ms) and the Mean Differences (95% CI) of the SEPs Within the Patients With ALL After Induction Therapy (A) and after CNS Therapy (B), as Well as Differences Between the Patients after CNS therapy (B) and their Age, Sex, and Height-Matched Controls (C)

	Patients (A) (N = 34)	Patients (B) (N = 38)	Difference[a] B-A (95% CI)	*P*	Control (C) (N = 38)	Difference B-C (95% CI)	*P**
Spinal Th12 to cortex (SP-P40)	19.6 (2.7)	21.0 (3.2)	1.4 (0.4 to 2.5)	0.011	19.6 (2.8)	1.4 (0.4 to 2.5)	0.009
Spinal C7 to cortex (N13-N20)	6.6 (0.9)	6.9 (1.2)	0.1 (−0.2 to 0.5)	0.43	7.1 (1.5)	−0.1 (−0.8 to 0.5)	0.65
Brain stem to cortex (P15-N20)	4.1 (1.1)	4.4 (1.0)	0.2 (−0.2 to 0.6)	0.29	4.5 (1.1)	−0.1 (−0.6 to 0.4)	0.59
Plexus to spinal C7 (EP-N13)	3.7 (0.5)	3.6 (0.7)	−0.1 (−0.2 to 0.3)	0.70	3.7 (0.5)	−0.03 (−0.3 to 0.3)	0.85
Wrist to brain stem (P15)	11.9 (1.4)	12.3 (1.5)	0.3 (−0.03 to 0.6)	0.07	11.8 (1.4)	0.5 (0.1 to 0.9)	0.029
Wrist to cortex (N20)	16.0 (1.2)	16.6 (1.4)	0.5 (0.2 to 0.8)	0.0013	16.3 (1.6)	0.3 (−0.3 to 0.9)	0.29

**P* = Significance level, tested with paired *t* test.
[a]Based on those 34 patients with data at both measurements.

thy is also associated with intrathecal methotrexate therapy, systemic chemotherapy, and cranial irradiation [24]. Earlier reports are restricted to patients with serious symptoms of myelopathy or encephalopathy. Our results reveal spinal cord dysfunction in patients with ALL after receiving intrathecal methotrexate and concomitant intravenous methotrexate therapy. Conduction from the spinal Th12 level to the cortex in the tibial nerve SEP was significantly delayed, but no significantly impaired conduction was observed from the brain stem to the cortex in the median nerve SEP. These findings support mainly a spinal dysfunction.

Exact clinical neurological examinations of the side effects due to chemotherapy or CNS therapy are difficult to perform, because children with ALL are very young, the peak incidence being in the first 5 years of life. The SEP method is a noninvasive, objective, and quantitative tool for examining and localizing neurological lesions in both the peripheral and CNS tissues [25–27]. Within the CNS, SEP provides a sensitive tool for the assessment of the spinal and brain stem posterior columns and medial lemniscal tracts and nearby structures. SEP abnormalities can be associated with demyelination and with axonal and neuronal loss. Demyelination produces latency prolongation while axonal loss reduces the amplitudes of the SEP [16]. We used this method to examine possible disturbances of impulse conduction in the spinal cord after the intrathecal therapy of methotrexate and in the intracranial somatosensory pathways during CNS therapy. The impulse conduction in the spinal cord measured by SEP has been earlier demonstrated to deteriorate after irradiation of the thorax in patients suffering from lung cancer without clinical signs of myelopathy [28].

We suppose that intrathecal methotrexate therapy is responsible for the spinal conduction delays observed here. Burch et al. [29] observed that tritiated methotrexate intrathecally penetrates the spinal cord quickly in animal studies so that a majority of the total area of spinal cord sections were exposed to the intrathecally administered drug within 1 hour. They observed high drug levels in the spinal areas corresponding to the location of pathological-anatomical findings, microvacuolation, and axonal swelling seen in the spinal cords of patients with paraplegia after intrathecal chemotherapy. Gilbert et al. [30] have shown that methotrexate primarily caused neuron toxicity in cerebellar explants from rats and axonal loss was seen after 2 weeks of exposure to methotrexate while an increase in the concentration of myelin basic protein was noted after the third week of exposure. These findings suggest that neuronal loss leads to a secondary loss of myelin. An elevation of myelin basic protein has also been observed in the CSF of patients with ALL during ascending myelopathy after receiving intrathecal methotrexate therapy, indicating a demyelinative process [8]. Lumbar punctures were performed repeatedly in conjunction with intrathecal methotrexate therapy of our patients. The measurements of the spinal conduction from the Th12 level cranially are distinctly above the lumbar puncture level, and it is therefore quite probable that the punctures are not responsible for the delays observed in SEP conduction.

Methotrexate neurotoxicity has been observed to be related to elevated CSF concentrations in patients with CNS leukemia [31]. There was one patient with CNS leukemia at the time of diagnosis in our series, but she achieved remission and had no CNS relapses during or after the treatment of leukemia, nor did any other patient have a CNS relapse during these therapy phases. The SR patients received somewhat smaller doses of methotrexate than did the IR or HR patients, but an exact evaluation of the dose dependence of methotrexate neurotoxicity was not possible because of the limited number of patients in these therapy groups.

The gross motor disturbances observed in our patients were thought to be caused mainly by a vincristine sensorymotor neuropathy in these therapy phases [15]. This was supported by the evaluation that the delays in the peripheral conduction time in the median and tibial nerve SEPs measured in these patients and reported separately [21] were related to vincristine therapy. A spinal cord dysfunction or brain tissue impairment may, however, partly explain these motor difficulties. Walking difficulties due to

myelopathy and motor clumsiness and weakness due to vincristine neuropathy affecting the peripheral nerves are manifested simultaneously and a clinical diagnosis to differentiate the level affected is therefore very difficult to establish.

In addition to the above, CNS therapy is directed to the brain tissue and therefore plays its own role in deteriorating the function of the sensory pathways and cortex. The intracranial central conduction measured via median nerve SEPs was not significantly delayed, but the amplitudes of the median nerve cortical SEPs were significantly decreased in the SR patients after the CNS therapy, which included both intravenous and intrathecal methotrexate medication. This amplitude reduction may be due to axonal/neuronal loss in the somatosensory pathways or sensory cortex. The CNS affect of chemotherapy is also supported by the finding that cortical function is disturbed in positron emission tomography during intrathecal and intravenous chemotherapy in children with ALL [32]. Chemotherapy is known to have an effect on the white matter of the brain, which lesions are transient in nature and are seen at 15 weeks after methotrexate treatment in magnetic resonance imaging of children treated for ALL [33,34]. The pathogenesis of these myelin lesions is supposed to be a toxic edema or a demyelinating process [33]. The recordings of the SEPs in our SR patients were performed immediately after receiving high doses of intravenous methotrexate therapy and therefore the intracranial central conduction times were possibly not yet distinctly delayed in this patient group.

Intracranial SEP conduction was not significantly delayed in the IR and HR patients 4 months after intravenous and intrathecal methotrexate therapy and 5–8 weeks after cranial irradiation. A subacute reaction to irradiation manifests a few weeks after radiation therapy and is known as somnolence syndrome [35,36]. This was observed in 60% of our patients [15]. Controversies have arisen concerning the pathogenesis and clinical significance of this syndrome, while our results suggest that it is not demyelinative in origin. Some authors have supposed that it is caused by transient defects in myelin synthesis, while others assume that it arises from cerebral edema, as corticosteroids have achieved a beneficial response [35,37]. The delayed adverse effects of radiation on nervous tissue are known to appear from a few months to years after irradiation [20,22]. Further follow-up is required to detect possible permanent conduction delays after chemotherapy and cranial irradiation. The slowing of cortical auditory evoked potentials secondary to white matter damage has also been shown in survivors treated with intensive CNS therapy a few years ago, especially with cranial irradiation [38]. Visual pathways investigated by visual evoked potentials have been observed to become impaired a few months after CNS therapy in children with leukemia [39].

At present, as the survival rates for ALL improve, the time has come to examine the milder side effects of chemotherapy and to consider the doses and time intervals appropriate in methotrexate therapy. Both clinically and methodologically, neurological symptoms and findings are difficult to localize, as it is difficult to determine their origin (i.e., from the brain or spinal cord level), especially in children. The SEP offers one possible method of effectively monitoring the side effects of therapy within the CNS.

In conclusion, intrathecal methotrexate and systemic chemotherapy cause abnormalities in somatosensory pathways within the CNS, suggesting also spinal cord dysfunction in children treated for ALL. Further studies will be needed to reveal how permanent these SEP abnormalities are and to what extent they are connected with clinical late effects.

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